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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,535	09/22/2003	Hideki Ichikawa	2923-0562	5882

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,535	ICHIKAWA ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/355,551.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0903*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1–14 are pending and being examined.

Priority

Under 35 U.S.C. 120, the claims in a U.S. application are entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claim is disclosed in the manner provided by 35 U.S.C. 112, first paragraph in the earlier filed application. Under 35 U.S.C. 119 (a) or (e), the claims in a U.S. application are entitled to the benefit of a foreign priority date or the filing date of a provisional application if the corresponding foreign application or provisional application supports the claims in the manner required by 35 U.S.C. 112, first paragraph.

In the present case the subject matter of claims 8–11 was not disclosed in the manner provided by 35 U.S.C. 112, first paragraph in the earlier filed 09/355,551 application, and the corresponding foreign application does not support claims 8–11 in the manner required by 35 U.S.C. 112, first paragraph. Accordingly, the effective filing date of claims 8–11 is 09/22/2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1–7 and 12–14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099) in view of Ron (U. S. Patent No. 5,171,579) and Avis (1990).

Neidhardt teaches osteogenic protein MP52 (see SEQ ID NOs: 1 and 3), the recombinant

production thereof (paragraph bridging pages 6-7 through paragraph bridging pages 7-8), and a pharmaceutical composition comprising same for bone healing (page 9, full paragraph 1). The limitation "produced by a means of genetic engineering technology" is a product-by-process limitation. If the MP52 produced by the process is the same as or obvious from Neidhardt's MP52, the MP52 is unpatentable even though it may have been made by a different process because the process limitation is not viewed as positively limiting the MP52, as it is assumed that equivalent products are obtainable by multiple routes. The burden is upon the applicants to establish a patentable distinction between the MP52 produced by the process and Neidhardt's MP52. Neidhardt does not teach lyophilization of MP52 in the presence of mannitol.

Ron teaches that osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution (including reconstitution from a lyophilized form). It is optimal to solubilize the osteogenic protein at concentrations of at least about 2 mg/ml, preferably about 4 mg/ml, so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary (column 2, lines 22-29). Ron teaches that additional optional components useful in the practice of the subject application include, e.g. cryogenic protectors such as mannitol (to protect from degradation during lyophilization), preservatives, antioxidants, etc. (column 4, lines 45-48). Ron's preferred osteogenic protein is recombinant BMP-2, but any isolated or recombinant osteogenic proteins of the TGF-β family would be similarly useful (column 1, lines 13-34 and 63-65; and column 2, lines 12-14 and 22-24).

Avis teaches that the particular advantages of freeze-drying (lyophilization) are ease of processing a liquid, pharmaceuticals can be stored in a dry state in which there are relatively few stability problems, the products are often more soluble and/or more rapidly soluble, and

dispersions are stabilized throughout their shelf-life (page 1565, paragraph bridging columns 1-2, through column 2, full paragraph 1). Avis teaches that mannitol has been found to be most useful to increase the solids content of the original solution to between approximately 5 and 25% so that the freeze-dried product plug occupies essentially the same volume as that of the original solution (page 1566, column 2, full paragraphs 1-3). A 5 to 25% mannitol solution contains 50 to 250 mg mannitol per ml.

Ron and Avis do not teach lyophilization of MP52 in the presence of mannitol.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising recombinantly produced MP52, as taught by Neidhardt, and to modify that teaching by making an osteogenic protein in the form of a pharmaceutically acceptable solution (including reconstitution from a lyophilized form), wherein the osteogenic protein is solubilized at a concentration of at least about 2 to 4 mg/ml, said solution further comprising cryogenic protectors such as mannitol, as taught by Ron, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because it is optimal to solubilize osteogenic proteins at a concentration of at least about 2 to 4 mg/ml so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary, and because cryogenic protectors, such as mannitol, protect from degradation during lyophilization. It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to add mannitol to a purified solution of human MP52 in an amount to give a mixing ratio of 2 to 4 mg/ml MP52 to 50 to 250 mg/ml mannitol and then lyophilize the resultant mixed solution with a reasonable expectation of success. In so doing, one would obtain a solution

comprising MP52 and mannitol, wherein the concentration of mannitol is 0.5-5% (w/v). One of ordinary skill in the art would have been further motivated to make this modification because the particular advantages of freeze-drying (lyophilization) are ease of processing a liquid, pharmaceuticals can be stored in a dry state in which there are relatively few stability problems, the products are often more soluble and/or more rapidly soluble, dispersions are stabilized throughout their shelf-life, and because mannitol has been found to be most useful to increase the solids content of the original solution to between approximately 5 and 25% so that the freeze-dried product plug occupies essentially the same volume as that of the original solution. A solution comprising 2 to 4 mg/ml MP52 and 50 to 250 mg/ml mannitol is a solution comprising MP52 and mannitol in the range of 1 : 5-50 (ratio by weight). A lyophilized form of said solution is a composition comprising MP52 and mannitol in the range of 1 : 5-50 (ratio by weight).

Regarding the limitations "prevention of coloration," "prevention of shrinking," and "prevention of aggregation," *prima facie* obviousness does not require that the prior references suggest combining their disclosure for the same reasons that Applicants combined them. Ron specifically suggest using mannitol as a cryoprotectant to prevent degradation of BMPs during the lyophilization process, which fairly suggest using mannitol during lyophilization of MP52 (a member of the same osteogenic protein family as BMPs). It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to prevent degradation as much as possible for as long as possible in order to have an as potent as possible for as long as possible MP52 biologic or pharmaceutical, which is motivation to prevent degradation by adding mannitol in accordance with the teachings of Ron. Furthermore, the examiner does not agree

that these results would have been unexpected to one skilled in the art. Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art. According to Avis, one skilled in the art of lyophilization typically considers "the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted before use, [as well as] the characteristics of the dried plug" (Avis, page 1566), when formulating a pharmaceutical or biological product, i.e., "whether the lyophilized substance will be dull or spongy or sparkling and crystalline, firm or friable, expanded or shrunken, etc." (*id.*). It is fair to say that Avis identifies the choice of excipient as a "result effective variable." Identification of mannitol as the ideal lyophilization excipient for MP52 would have been within the ordinary skill of the art.

The invention is prima facie obvious over the prior art.

Claims 7–14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099) in view of Ron (U. S. Patent No. 5,171,579) and Avis (1990) as applied to claims 7 and 12–14 above and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30).

Neidhardt in view of Ron and Avis teach a solution comprising MP52 and mannitol and a lyophilized form of said solution, as discussed above. Neidhardt in view of Ron and Avis do not teach a solution comprising MP52 and mannitol and a lyophilized form of said solution, wherein said solution comprises a surfactant.

Chang teaches that the addition of small amounts of surface-active agents protected proteins from both freeze- and surface-induced denaturation (Abstract). Freezing plays a

crucial role in the damage incurred by proteins during freeze-drying (page 1325, left column, full paragraph 1). It has been found with a few proteins that low concentrations of surfactants (i.e., below the critical micellar concentration), which would not be expected to greatly alter the free energy of protein denaturation, provide a high degree of protection during freeze-thawing. Surfactants are known to stabilize proteins against surface-induced denaturation, so these results also suggest that the ice-water interface can contribute to freeze-induced protein denaturation. See page 1325, right column, full paragraph 1. Chang's results indicate that the freezing-induced denaturation is related to the exposure of proteins to an ice-water interface, so it seems rational to use surfactants as cryoprotectants (page 1327, right column, full paragraph 2). The capacity of 0.01% Tween 80 to protect proteins during freeze-thawing appears to be quite general because all of the model proteins were essentially completely protected (paragraph bridging pages 1327-1328). To determine how general this protective effect was, the influence of several surfactants, with different chemical structures, on freeze denaturation of LDH was tested. All the tested surfactants protected LDH from precipitation during a quench-freezing process, even though the control frozen without a surfactant showed a significant increase in turbidity (Table 2). See page 1328, left column, full paragraph 1. The surfactants tested included Tween, Triton, and Brij. See page 1328, Table 2. This general stabilization of proteins during freeze-thawing by relatively low concentrations of surfactants strongly supports the contention that damage to proteins during freezing is due, at least to a large degree, to surface denaturation (page 1328, left column, full paragraph 2). In general, it appears that to obtain native, nonaggregated protein after freeze-drying and rehydration, it is necessary to develop a formulation that protects the protein during both freezing and drying. When 0.1% of

Tween 80 was included in the protein solution, the soluble aggregate content decreased to 3%. Inclusion of 1% sucrose in the formulation, which is known inhibit unfolding of proteins during freeze-drying, led to slightly less protection, as reflected by a 8% aggregate content upon reconstitution. See paragraph bridging pages 1328-1329. To ascertain at what point during the freeze-drying and rehydration process Tween 80 was providing its beneficial effects, Chang conducted the following experiments. First, Chang found that the surfactant can prevent the formation of aggregates during rehydration. When the protein was freeze dried without surfactant but reconstituted with 0.1% Tween 80, the aggregate content was reduced to 23%. However, this protection was not sufficient to explain the reduction of aggregate content to 3% when Tween 80 was included prior to the freeze-drying. See page 1329, left column, full paragraph 1. Thus, for the rational design of stable protein formulations for freezing and freeze-drying, it is advantageous to include a surfactant, which apparently inhibits the denaturation of proteins during freezing. A surfactant may only be sufficient to protect proteins during the freezing step. Another stabilizer, which is known to confer protection during drying (e.g., sucrose) will probably be needed to completely inhibit protein unfolding during freeze-drying. See page 1329, right column, last paragraph. Freeze-drying of IL-1ra solutions was performed as follows. An IL-1ra solution containing 2 mM potassium phosphate buffer, 3% mannitol, and 1 or 100 mg/mL of protein was prepared by dialysis. Mannitol was included as a crystalline bulking agent. Addition of 1% (w/v) sucrose or 0.1% (w/v) Tween 80 was made after the dialysis. Each vial was frozen by immersion into liquid nitrogen and loaded onto a shelf that was prechilled to -50 °C. After 1 h at -50 °C, the shelf temperature was increased to -15 °C at a rate of 1 °C/h. After an additional hour of incubation of the vials at this temperature, drying

was initiated by decreasing the chamber pressure to 100 μmHg. Then, the shelf temperature was increased to 25 °C at a rate of 1 °C/min. After completion of a 10-h drying cycle under vacuum the vial head spaces were filled with dry gaseous nitrogen. The vials were capped with stoppers until further analysis. See page 1326, left column, full paragraph 4. It is fair to say that Chang identifies the addition of surfactants and their combination with another stabilizer which is known to confer protection during drying, as a "result effective variable" for inhibiting protein denaturation during freeze-drying. Chang does not teach a lyophilized composition comprising MP52 and mannitol, a process for the preparation of said composition, a solution comprising MP52 and mannitol, or said solution further comprising a detergent/substance.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make teach a solution comprising MP52 and mannitol and a lyophilized form of said solution, as Neidhardt in view of Ron and Avis, and to modify that teaching by adding a surfactant, as taught by Chang, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because for the rational design of stable protein formulations for freezing and freeze-drying, it is advantageous to include a surfactant, which apparently inhibits the denaturation of proteins during freezing. The invention is prima facie obvious over the prior art.

Claims 7–10 and 12–14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099), Ron (U. S. Patent No. 5,171,579), and Avis (1990) as applied to claims 7 and 12–14 above and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30) and further in view of Hansen (U. S. Patent No. 6,586,574) and in light of the MeSH

definition of "poloxamer."

Neidhardt in view of Ron and Avis and further in view of Chang teach a solution comprising MP52, mannitol, and a surfactant, as discussed above. Neidhardt in view of Ron and Avis and further in view of Chang do not teach a solution comprising MP52, mannitol, and a polyoxyethylene-polyoxypropylene copolymer.

Hansen relates generally to the stabilization of freeze-dried proteins. Hansen discloses that further stabilization of freeze-dried proteins can be obtained by the addition of surfactants, such as Tween and poloxamers (column 6, full paragraph 3). Poloxamers are polyoxyethylene-polyoxypropylene copolymers, as evidenced by the MeSH definition of "poloxamer." The term "surfactants" generally include those agents, which protect the protein from air/solution interface-induced stresses and solution/surface induced-stresses (e.g. resulting in protein aggregation), and may include detergents such as polysorbate, poloxamer or polyethylene glycol, and the like. Optionally, concentrations from about 0.01% to about 1% (w/w) are suitable for maintaining protein stability, however, the levels used in actual practice are customarily limited by clinical practice. See column 5, full paragraph 2. Hansen does not teach a solution comprising MP52, mannitol, and a polyoxyethylene-polyoxypropylene copolymer.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a solution comprising MP52, mannitol, and a surfactant, as taught by Neidhardt in view of Ron and Avis and further in view of Chang, and to modify that teaching by making a solution comprising MP52, mannitol, and a poloxamer, as taught by Hansen, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because further stabilization of freeze-dried proteins can be

obtained by the addition of surfactants, such as poloxamers. The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 are indefinite over the recitation of "detergent/substance" and/or "polyoxyethylenic detergent/substance" because it is unclear if the solution further comprises a detergent and/or a detergent substance or a non-detergent substance, a polyoxyethylenic detergent and/or a polyoxyethylenic detergent substance or a polyoxyethylenic non-detergent substance. The metes and bounds are not clearly set forth.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JUNE 24, 2006